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Original Research Article

MRI guided online adaptive radiotherapy and the dosimetric impact of inter- and intrafractional motion in patients with cervical cancer

Shouliang Ding [a,b,1], Zun Piao [a,1], Meining Chen [a,1], Fanghua Li [a], Yongbao Li [a], Biaoshui Liu [a], Hongdong Liu [a,*], Xiaoyan Huang [a,b,*], Junyun Li [a,*]

[a] State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou 510060, PR China

[b] United Laboratory of Frontier Radiotherapy Technology of Sun Yat-sen University & Chinese Academy of Sciences Ion Medical Technology Co., Ltd, Guangzhou 510060, PR China

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ABSTRACT

Purpose: The aim of this study was to evaluate the inter- and intrafractional organs motions and dosimetric advantages of MRI guided online adaptive radiotherapy for cervical cancer.

Methods: A total of 150 fractions treated on the 1.5 T Unity MR-Linac were included in this study. Each fraction, pre-treatment, position validation and post-treatment MRI scans were obtained. Structures including CTV, rectum and bladder were delineated by the same radiation oncologists on each MRI. The inter- and intrafractional changes of contours were assessed by Hausdorff distance (HD), dice similarity coefficient (DSC), relative volume difference (ΔV) and the relative positions of the geometric center. The non-ART plans and online adaptive plans were obtained by recalculating or re-optimizing from reference plans on daily MRI, respectively. CTV coverage and OARs constraints were evaluated between ART and non-ART plans.

Results: For each fraction, the interfractional changes of HD, ΔV and DSC for CTV, bladder and rectum were significant. Our study also examined the relationship of bladder and rectum filling on CTV position. For 150 non-ART plans, CTV coverage constraints ($D_{98\%} \geq 45$ Gy) were not met by 45 %, while 15 % were not covered by more than 5 % of the prescribed dose. Compared to the non-ART plans, the ART plans had higher CTV coverage and lower dose to the bladder and rectum ($P < 0.05$). During the treatment, the intrafractional changes of bladder, rectum and CTV may affect actual dose delivery. And we observed an intrafractional time trend in the motion of the CTV. There were 15 % fractions failing the CTV coverage constraints in post-MRI due to intrafractional motion. The adaptive plans optimized with 3 mm margin could cover CTV of post-MRI in 98 % fractions.

Conclusions: Considerable inter- and intrafractional CTV and OARs changes were observed in cervical cancer patients treated on MR-Linac. MRI guided online ART has significant dosimetric advantages in cervical cancer and is an ideal approach for achieving individualized and precise radiotherapy.

Background

Locally advanced cervical cancer has been treated with concomitant external radiation therapy and chemotherapy, followed by brachytherapy for a boost to the primary tumor [1]. Intensity-modulated radiation therapy (IMRT) demonstrates promise as a treatment modality for minimizing radiation exposure to healthy tissue in women with gynecologic malignancies when compared to conventional and conformal techniques [2,3]. Preliminary clinical findings reveal a marked decrease in both immediate hematological effects and subsequent gastrointestinal complications with the application of IMRT [4,5].

However, during the treatment of cervical cancer patients, the position and shape of target volumes change due to internal organ motion and tumor regression [6,7], may create an adverse effect on highly conformal IMRT. In conventional radiotherapy process, to accommodate these inevitable variations, relatively extensive planning target volume

* Corresponding authors at: State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou 510060, PR China (X. Huang).

E-mail addresses: liuhd@sysucc.org.cn (H. Liu), huangxiaoy@sysucc.org.cn (X. Huang), lijuny@sysucc.org.cn (J. Li).

[1] These authors contributed equally to this work.

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(PTV) margins are necessitated [8,9], which may lead to irradiating a considerable volume of healthy tissues.

Recently, the innovative application of MRI-guided online adaptive radiotherapy (MRIgOART) has piqued the interest of numerous oncologists worldwide. This cutting-edge technology uniquely empowers the real-time adjustment of dose distribution, thereby mitigating potential variations within treatment regions [10]. Our previous study has demonstrated the synthetic CT (sCT) generated with bulk rED assignment approach guarantees an acceptable level of dose accuracy for cervix carcinoma patients with 1.5 T MR-Linac [11]. MRI is superior for delineation of target structures in the gynecological site. In addition, daily session MRI can be used to track inter- and intrafractional organ motion during the treatment. As a result, MRIgOART technology could correct the anatomical changes potentially and therefore reduce the healthy tissue involvement as well as escalate the target dose, which is the new breakthrough in radiotherapy for normal tissue protection and disease control.

This research is designed to achieve two interrelated objectives: (1) to investigate the inter- and intrafractional variations of the clinical target volume (CTV), bladder and rectum during treatment on MR-Linac. (2) to demonstrate the potential dosimetric benefits of MRI-gOART in cervical cancer patients.

Materials and methods

Patients data

This retrospective study encompassed six cervical cancer patients treated on the Elekta 1.5 T MR-Linac at our department from 2019.9 to 2020.2. The stage was executed in accordance with the International Federation of Gynecology and Obstetrics (FIGO) classification system. In accordance with our treatment protocol, all the patients were treated with IMRT. The 1.5 T Elekta MR-Linac, due to the construction of the system will have a maximum radiation field size in the superior-inferior patient direction of 22 cm at isocentre. In this study, cervical cancer patients undergoing radiation therapy did not have lymph node metastases, with prescription dose of 45 Gy in 25 fractions.

Patient treatment workflow

The treatment workflow for each fraction is illustrated in the Fig. 1. The pre-treatment MR (pre-MRI) T2-weighted MRI scan was performed using 3D spoiled gradient recalled acquisition in steady state (3D SPGR), with a flip angle of 90°, echo time (TE) of 278 ms, repetition time (TR) of 1535 ms, then seamlessly imported into the online Monaco TPS. Then, the adapt to shape (ATS) or adapt to position (ATP) workflow was applied depending on the clinical situation of the day. The first option was ATP, where the shape and weight of beam segments in the reference plan were adjusted to match the current position of targets and OARs. Thus, ATP is an alternative to move the treatment table, which is fixed during a treatment session, and was used if there were relatively modest changes to the anatomy compared with the reference plan. The second option was ATS, where a new adapted plan was generated to match the anatomy of the day for contour propagation from the reference plan to the session MRI. For ATP, the dose calculation of the day was performed on the reference scan while the session MRI scan of the day was used for dose calculation for ATS. No corrections in beam angles were made between the reference plan and the adapted plan. The position validation MR (pv-MRI) scan was acquired during plan adaptation and used to make a visual exhaustive survey of the adapted plan. After beam on, the post-treatment MR (post-MRI) scan was acquired. All patients were treated by ATP, and the simulated ATS plans were generated in our study to do the retrospective analysis.

Delineation and contour analysis

We delineated the CTV, bladder and rectum on all MR scans. The delineation was performed by a radiation oncologist using the Monaco and evaluated by an experienced professor. The interfractional variations were characterized by assessing the volumetric discrepancies between each pre-MRI session and the initial simulation images. For each fraction, the differences of structure between pre-MRI and pv-MRI

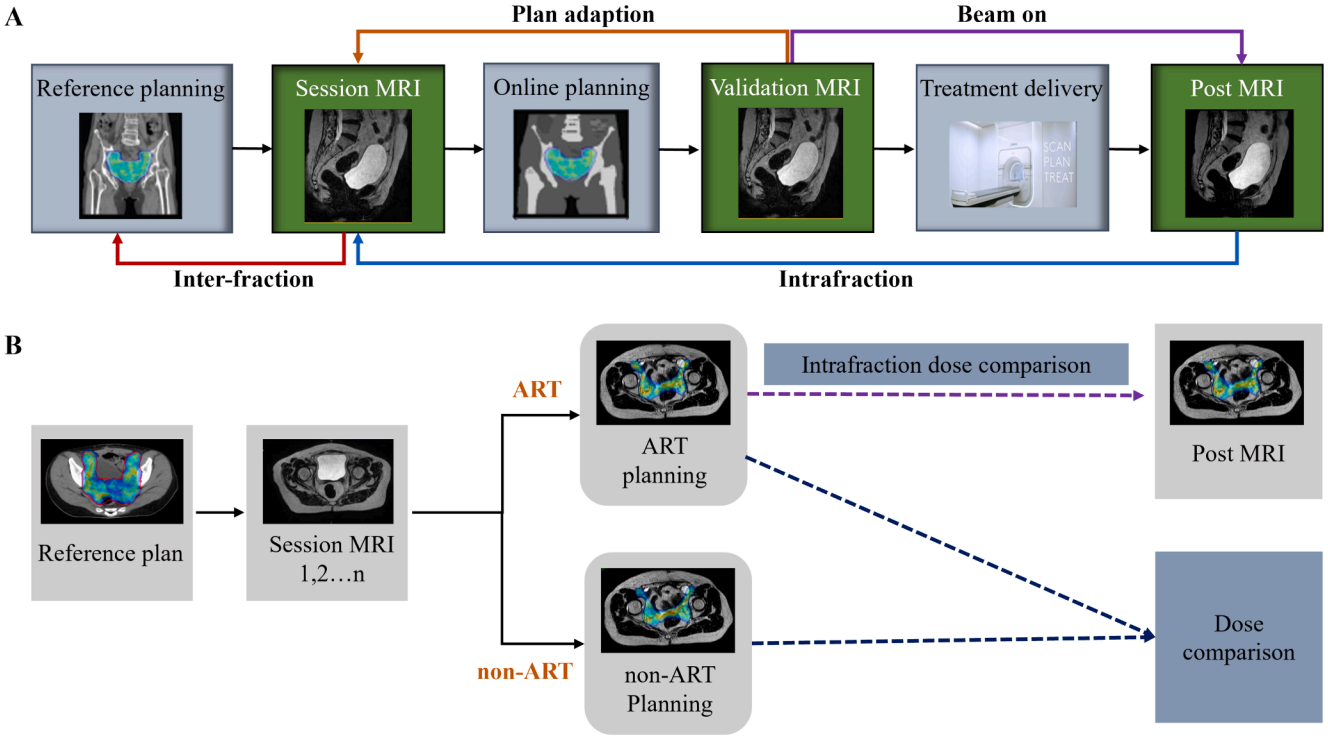

Fig. 1. Workflow used in this study to assess the variations of structures and dose in MRI guided online adaptive radiotherapy for cervical cancer treatment process.

evaluated the region of interest (ROI) changes during plan adaptation. The differences between pre-MRI and post-MRI evaluated the intrafractional changes. And the differences between pv-MRI and post-MRI evaluated the changes during delivery. To measure the variability of ROIs, the ensuing metrics were employed:

(1) Relative volume differences (ΔV) of ROIs on all the MR images. This differential quantifies the volume at the target image in relation to the benchmark volumes observed in the reference images

$$\Delta V = \frac{(V - V_{\text{reference}})}{V_{\text{reference}}} \times 100\%$$

(2) Dice similarity coefficient (DSC) quantifies the ratio of intersection between the two structures. The DSC is calculated as:

$$DSC = \frac{2(V_A \bigcap V_B)}{V_A + V_B}$$

where $V_A \bigcap V_B$ is the intersection of regions A and B. The DSC scale spans from 0 to 1, with a higher value signifying a greater extent of volume intersection.

(3) Hausdorff distance (HD) metrics revealed the greatest distance between reference and contours. HD is defined as:

$$HD(A,B) = max[h(A,B), h(B,A)]$$

$$h(A,B) = \max_{a \in A} \min_{b \in B} \|a - b\|$$

At its core, the HD quantifies the most mismatched distance of a point from A to B. If HD (A, B) = d, then every point within A must be within distance d of the nearest point with B and vice versa.

(4) The deviation changes in the relative positions of the geometric center of the CTV in the lateral (LAT/X), vertical(VRT/Y) and longitudinal(LNG/Z) directions: offset value = A (x, y, z) − B (x′, y′, z′).

Dosimetric variation and assessment

The reference treatment plans were generated using step-and-shoot IMRT and employing 9 beam groups on original CT. MRIgOART plans were created with the MRI datasets. The reference plan's delineations and electron density information of were propagated to the session MRI thereafter undergoing meticulous refinement by both the physicist and physician to guarantee the precision of electron density mapping and daily delineations. The reference plan was adjusted to accommodate the daily anatomical variations with the same optimization constraints and beam angles on the session MRI with adapted contours. In conventional plan, the PTV (expanded from CTV with margin of 7 mm) was optimized. While in ART treatment plan, the CTV was directly used for optimization. The inspiration behind this proposition stems from the prospect of significantly diminishing treatment uncertainties within the integrated online MR-Linac workflow. This innovative approach leverages the high soft-tissue contrast of MR images, accurate delineation of critical structures, and adaptation of treatment plan before each fraction.

And the reference plan was transfered into the session MRI datasets to create the non-ART plans. The radiation oncologists modified the structures on session MRI and physicists ensured the electron density mapping. Then, the reference plan was recalculated on the session MRI with the daily anatomy. For each case, the differences in dose to OARs and CTV coverage between the ART and non-ART plans were compared for each fraction.

Additionally, the differences of dose to target and OARs on post-MRI were utilized to evaluate the intrafractional dose changes. The intrafractional PTV (intraPTV) expanded from the CTV with 3 mm margin was used to correct intrafractional motions, and the ART plans were reoptimized with intraPTV.

Data statistics

To describe continuous data, we resorted to employing the mean and standard deviation (SD) or rang and median. While for categorical data, the frequency counts and percentages were used. All analyses were conducted employing SPSS (v25.0) (IBM Corporation, Armonk, NY, USA). Statistical analysis was carried out employing Wilcoxon signed rank test with a significance threshold set at $p < 0.05$.

Results

Interfractional changes of CTV, bladder and rectum

There were 150 fractions and 450 MR images evaluated in this study. The baseline characteristics were summarized in Table 1. For each fraction, in terms of volume, DSC and HD for the interfractional changes of CTV, bladder and rectum were significant. Compare to the Fx0, the mean interfractional ΔV, DSC and HD of CTV were 1.27 % (range: −11.09 % ~ 23.24 %), 0.88 (range: 0.81 ~ 0.98), and 19.28 mm (range: 9.46 ~ 30.95 mm), respectively. The relative deviation changes of the geometric center point of the CTV in the lateral (LAT/X), vertical(VRT/Y) and longitudinal(LNG/Z) directions were obvious (the deviation ranges in the X, Y, and Z directions were −3.4 ~ 0.6 mm, −6.0 ~ 2.6 mm, −3.7 ~ 4.7 mm). The changes of CTV for all cases were irregular. Compared to the Fx0, the mean interfractional ΔV, DSC and HD of bladder were −10.17 % (range: −87.93 % ~ 221.15 %), 0.68 (range: 0.22 ~ 0.91), and 30.58 mm (range: 9.15 ~ 83.59 mm), respectively. The most obvious changes were observed in bladder during treatment. Especially, the decrease in mean bladder volumes was from 315 to 261 cm^3 between the first and last weeks of treatment. Compared to the Fx0, the mean interfractional ΔV, DSC and HD of rectum were 21.01 % (range: −9.91 % ~ 94.44 %), 0.69 (range: 0.48 ~ 0.95), and 22.98 mm (range: 5.55 ~ 52.17 mm), respectively. As shown in Fig. 2, the CTV was affected by the volume changes of the bladder and rectum. Especially, the CTV with large changes had corresponding large changes in the bladder.

Intrafractional changes of CTV, bladder and rectum

The intrafractional changes were evaluated by the differences between pre-MRI and post-MRI. The result shows that the mean intrafractional ΔV, DSC and HD of CTV were −1.27 % (range: −13.39 % ~ 36.41 %), 0.95 (range: 0.85 ~ 0.98), and 9.53 mm (range: 3.56 ~ 27.23 mm), respectively. The relative deviation changes of the geometric center point of the CTV in the lateral (LAT/X), vertical(VRT/Y) and

Table 1
Patient and tumor characteristics.

Characteristics	Patient Number (n = 6)
Age at cervix cancer diagnosis (Median, range)	61 (56–70)
FIGO stage	
I b1	2
II a1	2
II a2	1
III b	1
Pre-treatment tumor size	267.83 cm^3 (232 ~ 324 cm^3)
Fraction tumor size	271.59 cm^3 (214.09 ~ 399.30 cm^3)
Prescription	45 Gy/25F
Radiotherapy technique	IMRT (step and shoot)
Beam number	9
Treatment time	18.96 min (13 ~ 34 min)

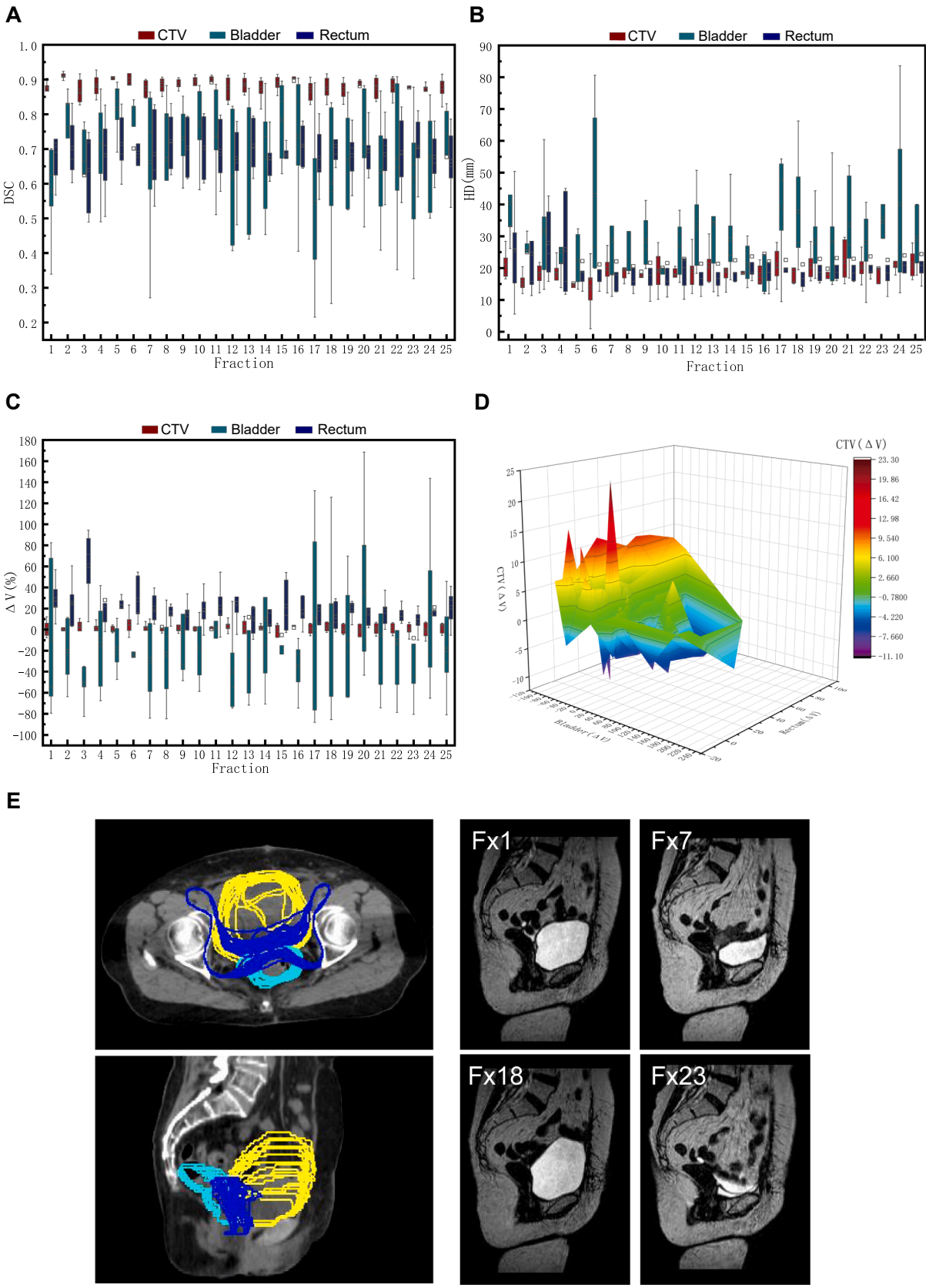

Fig. 2. The interfractional changes in CTV, bladder and rectum. (A) The DSC of CTV, bladder and rectum for all patients in each fraction. (B) The HD of CTV, bladder and rectum for all patients in each fraction. (C) The ΔV of CTV, bladder and rectum for all patients in each fraction. (D) The relationship of bladder and rectum filling on CTV volume. Axial slices of a representative case at planning (Fx0), fraction 1, 7, 18 and 23 (Fx1, Fx7, Fx18 and Fx23), illustrating patient-specific serial CTV, bladder and rectum changes. The CTV, bladder and rectum were contoured in blue-line, yellow-line and wathet-line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

longitudinal(LNG/Z) directions were −1.4 ~ 1.7 mm, −3.6 ~ 1.5 mm, −1.1 ~ 4.3 mm, respectively. The mean intrafractional ΔV, DSC and HD of bladder were 20.83 % (range: −3.86 % ~ 96.78 %), 0.89 (range: 0.67 ~ 0.98), and 14.52 mm (range: 4.38 ~ 50.51 mm). The mean intrafractional ΔV, DSC and HD of rectum were 0.15 % (range: −16.03 % ~ 18.48 %), 0.98 (range: 0.81 ~ 1), and 2.91 mm (range: 0 ~ 21.25 mm). The change of bladder volume was more obvious than that of the rectum, and the changes of CTV mainly depended on bladder. The mean treatment time for the fractions was 18.96 min (range: 13 ~ 34 min). As shown in Fig. 3, the intrafractional changes of bladder were affected by pre-treatment volume and treatment time. The ΔV value of bladder was close to 0 when the session treatment time is short and the pre-treatment bladder volume was large, while for a long treatment time and small pre-treatment volume, the corresponding intrafractional changes of bladder were manifest.

The changes of bladder and rectum during plan adaptation

For each fraction, the differences of structure between pre-MRI and pv-MRI were evaluated during plan adaptation. The mean time of plan adaptation was 11.84 min (range: 7 ~ 26 min). As depicted in Fig. 4**A**, the result shows that the mean ΔV, DSC and HD of bladder were −6.81 % (range: 0 ~ 44.57 %), 0.97 (range: 0.81 ~ 1), and 5.69 mm (range: 0 ~ 33.55 mm), respectively. The mean ΔV, DSC and HD of rectum were 0.29 % (range: −8.07 % ~ 13.47 %), 0.97 (range: 0.81 ~ 1), and 4.81 mm (range: 0 ~ 33.54 mm).

The changes of bladder and rectum during plan delivery

The differences between pv-MRI and post-MRI evaluated the changes during delivery. The mean time of plan delivery was 7.07 min (range: 4 ~ 15 min). As shown in Fig. 4**B**, the mean ΔV, DSC and HD of bladder were 8.17 % (range: −5.10 % ~ 43.91 %), 0.94 (range: 0.81 ~ 1), and 10.29 mm (range: 0 ~ 31.86 mm), respectively. The mean ΔV, DSC and HD of rectum were 0.09 % (range: −9.94 % ~ 7.85 %), 0.99 (range: 0.86 ~ 1), and 2.23 mm (range: 0 ~ 11.17 mm).

Dosimetric variation and assessment

Fig. 5 shows that dosimetric criteria between plan based on CTV and PTV. The dose coverage of CTV was similar between Plan-CTV and Plan-PTV, but the CTV based plans obviously had a reduced dose to bladder and rectum ($P < 0.05$). The result shows that ART treatment plan directly optimized with CTV is obviously advantageous.

There were 150 adaptive plans and 150 non-adaptive plans were analyzed in this study, as depicted in Figs. 6 and 7. For the 150 non-ART plans, 67 (45 %) of them failed in the CTV coverage constraints ($D_{98\%} \geq$ 45 Gy), 23 plans (15 %) failed by exceeding 5 % of prescribed dose coverage. For comparison, $D_{98\%}$ of CTV was maintained $\geq$ 45 Gy for all adaptive plans. Additionally, the mean dose of bladder and rectum were 33.86 ± 2.19 Gy and 41.52 ± 2.02 Gy in adaptive plans, respectively. For non-adaptive plans, the mean dose of bladder and rectum were 35.31 ± 2.35 Gy and 43.46 ± 2.09 Gy, respectively. Compared with the non-adaptive plans, the adaptive plans had higher CTV coverage and lower dose to OAR ($P < 0.05$).

The mean treatment time was 25.71 ± 6.73 min for Unity MR-Linac workflow. During the treatment, the intrafractional changes of bladder, rectum and CTV may affect actual dose delivery. In this study, the intrafractional dose changes were presented in Fig. 6. The mean changes of CTV $D_{98\%}$ were −0.27 ± 0.90 Gy and there were 22 (15 %) fractions with failed CTV coverage constraints ($D_{98\%} \geq$ 45 Gy) in post-MRI. The mean dose to bladder and rectum were −0.72 ± 0.94 Gy and 0.03 ± 0.20 Gy, respectively. To consider the intrafractional changes, we used a uniform 3 mm margin to create intraPTV. The results showed that the adaptive plans optimized with intraPTV could cover CTV of post-MRI in 147 (98 %) fractions.

Discussion

Over the past few years, IMRT for cervical cancer has gained significant traction owing to its promise of reduced side-effect while maintaining optimal tumor control. While the superior dosimetric performance and clinical effectiveness of IMRT in comparison to 3D conformal radiation is clear and consistent across literature, apprehension regarding geometric uncertainties due to unpredictable internal organ motions of both target and OARs, exists with IMRT [12]. Over time, the pelvic organs naturally undergo alterations in both position and volume. Consequently, the anatomy of the pelvis at the stage of radiotherapy planning may variate from its anatomy during the actual treatment period. These individual organ changes may result in variations in the position and shape of CTV.

While the organ motion in external beam radiotherapy for cervical cancer is well reported across the literature, most of the data is acquired by CBCT [12–14]. Organ motion patterns are patient specific, with some having very little (5 mm) and others having much larger shifts (40 mm) of the target volume [7]. MR images are superior in soft-tissue resolution and can be used to more accurately delineate pelvic organs [10,15]. In the present study, the interfractional variations of CTV, bladder and rectum were significant during treatment. The mean interfractional volume changes for CTV, bladder and rectum were 1.27 % (range: −11.09 % ~ 23.24 %), −10.17 % (range: −87.93 % ~ 221.15 %) and 21.01 % (range: −9.91 % ~ 94.44 %), respectively. It is clear from the prospective observation that interfractional variation in organ filling is inevitable, even with a pre-specified organ filling protocol [12]. While an exact threshold for acceptable levels of reproducibility remains undefined, our investigation provides insight regarding the magnitude of absolute variation in organ volume. Our study also examined the relationship of bladder and rectum filling on CTV position. Especially, the bladder filling played a major role in the CTV variations. This observation was similar to reports by Ghosh et al showing older age of patient and larger planning CT bladder volume lead to significant increase in bladder volume variability parameters [12]. Additionally, throughout the course of treatment, the bladder volume has been shown to systematically decrease with a mean reduction of 17.1 % in bladder volume from the first to last week, which is probably due to the radiation cystitis and reduced bladder capacity. The reported extent of systemic bladder volume reduction in existing literature is in the range of ~50 % to 71 % [16,17], a much lesser extent is seen in the present study. Ghosh et al also showed an absolute reduction of 16.3 % in mean bladder volume from the first to fifth week [12].

The complex dose distribution attained through IMRT, especially its nuanced hollows and strikingly steep dose gradients, necessitate a reevaluation of the potential implications of internal organ dynamics to be revisited to avoid treatment misalignment. The most widely adopted approach in IMRT for cervical cancer treatment involves a single anisotropic tapered margin [7]. The CTV-PTV margin encompasses two distinct elements: the set-up margin accounted for patient set-up and delivery errors, and the internal margin accounted for organ motion. However, target coverage cannot be perfectly assured with such approaches, as shown by Tyagi et al, where a uniform isotropic margin of 15 mm failed to encompass CTV in 32 % fractions [14]. While Gordon et al. [18] suggested that with a large single anisotropic margin approach, an unavoidable dose increase in OAR is inevitable.

ART is an ideal approach to correct these variations in dosing regions. The MRI guided online ART (MRIgOART) can create the online adaptive treatment plans optimized based on the anatomy and contours on daily MR images [19]. In this study, the CTV was directly used for optimization in ART treatment plan. The inspiration behind this proposition stems from the prospect of significantly diminishing treatment uncertainties within the integrated online MR-Linac workflow. This innovative approach leverages the high soft-tissue contrast of MR images, accurate delineation of critical structures, and adaptation of treatment plan before each fraction. The conventional PTV was created

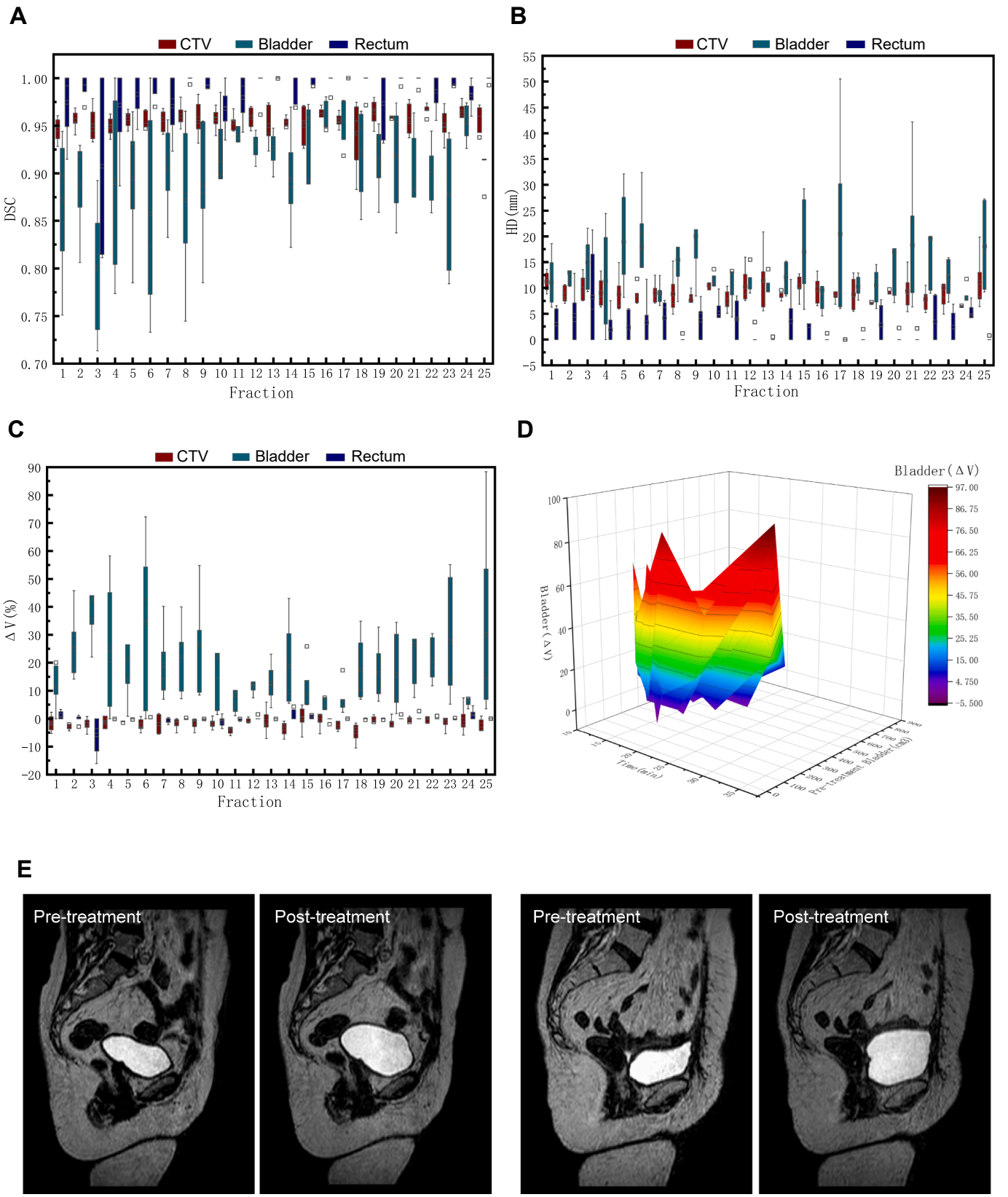

Fig. 3. The intrafractional changes in CTV, bladder and rectum. (A) The DSC of CTV, bladder and rectum for all patients in each fraction. (B) The HD of CTV, bladder and rectum for all patients in each fraction. (C) The ΔV of CTV, bladder and rectum for all patients in each fraction. (D) The relationship of treatment time and pre-treatment bladder filling on bladder intrafraction changes. (E) Pre-treatment and post-treatment axial slices of two cases.

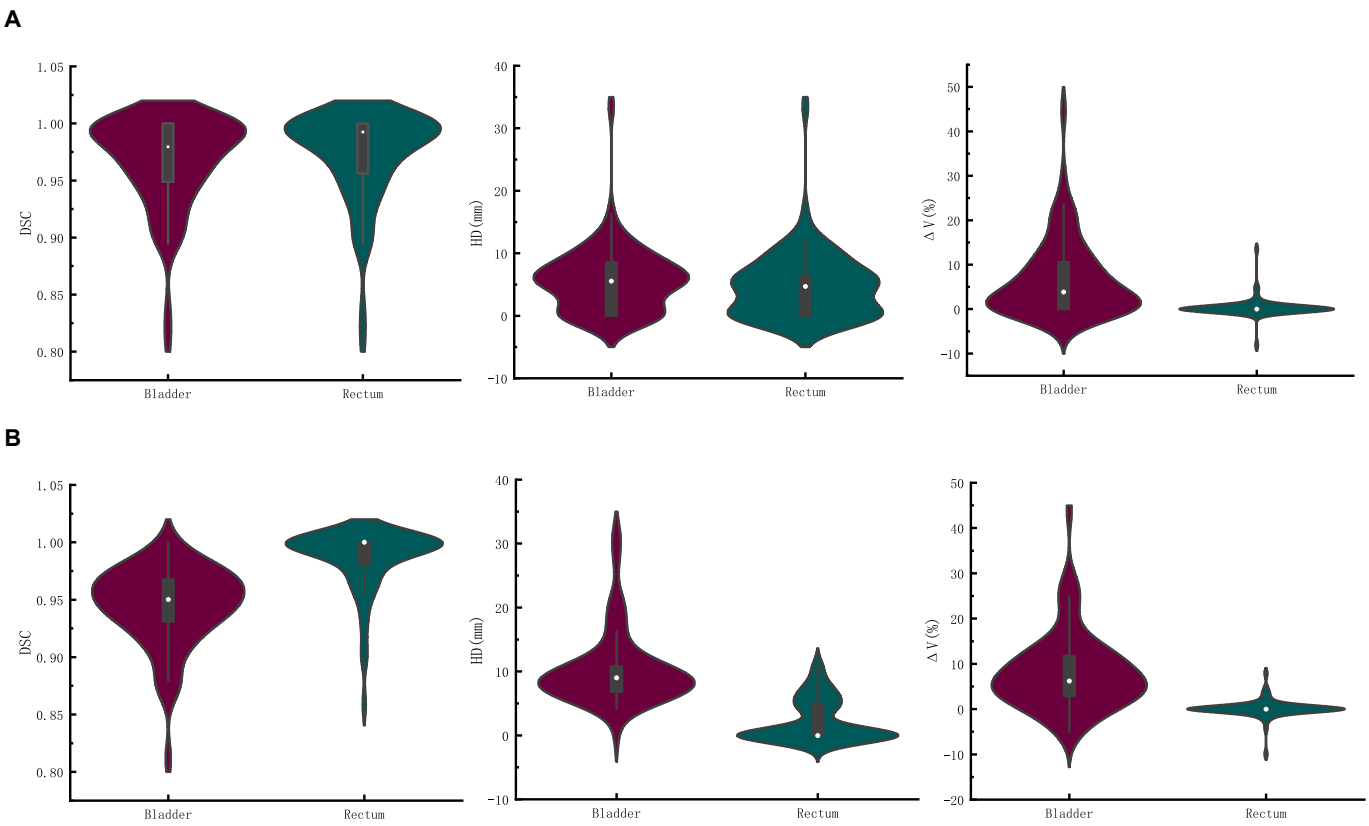

Fig. 4. The changes of bladder and rectum during plan adaption and delivery. (A) DSC, HD and ΔV of bladder and rectum during plan adaption. (B) DSC, HD and ΔV of bladder and rectum during delivery.

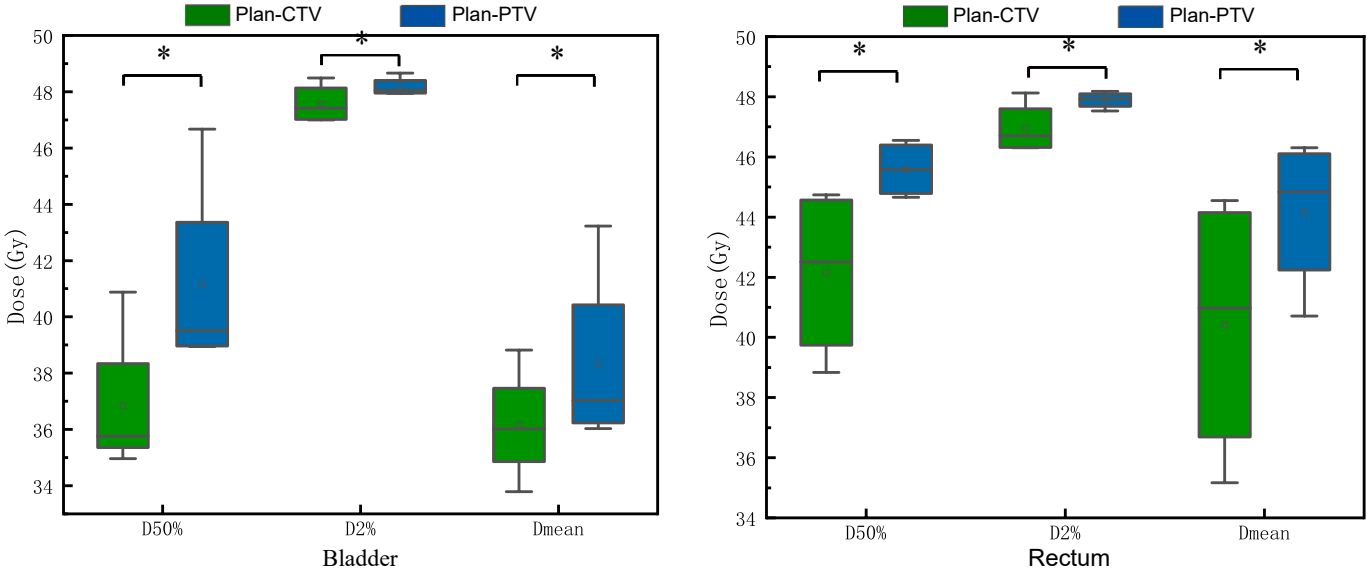

Fig. 5. The dosimetric comparison of bladder and rectum between Plan-CTV and Plan-PTV. A * indicates a significance of $P < 0.05$.

from expending the CTV with margin of 7 mm in the study. The dose coverage of CTV was similar between Plan-CTV and Plan-PTV, but the CTV based plans obviously reduced the dose to bladder and rectum ($P < 0.05$). And for 150 non-ART plans, there were 45 % with failed CTV coverage constraints ($D_{98\%} \geq 45$ Gy), with 23 plans (15 %) failed by more than 5 % of prescribed dose coverage. Compared to the non-ART plans, the ART plans had higher CTV coverage and lower dose to the bladder and rectum ($P < 0.05$). Therefore, the daily MRIgOART could be useful and valuable for patients with cervical cancers. The lower dose to OARs by adaptive plan might be able to reduce acute and late gastrointestinal (GI) and genitourinary (GU) toxicities [3]. The results showed that MRIgOART could potentially reduce side-effects without compromising tumor control.

However, the MRIgOART workflow is highly complicated and needs more time to prepare for treatment delivery than conventional radiotherapy [20]. The mean time of one treatment session (on-table time

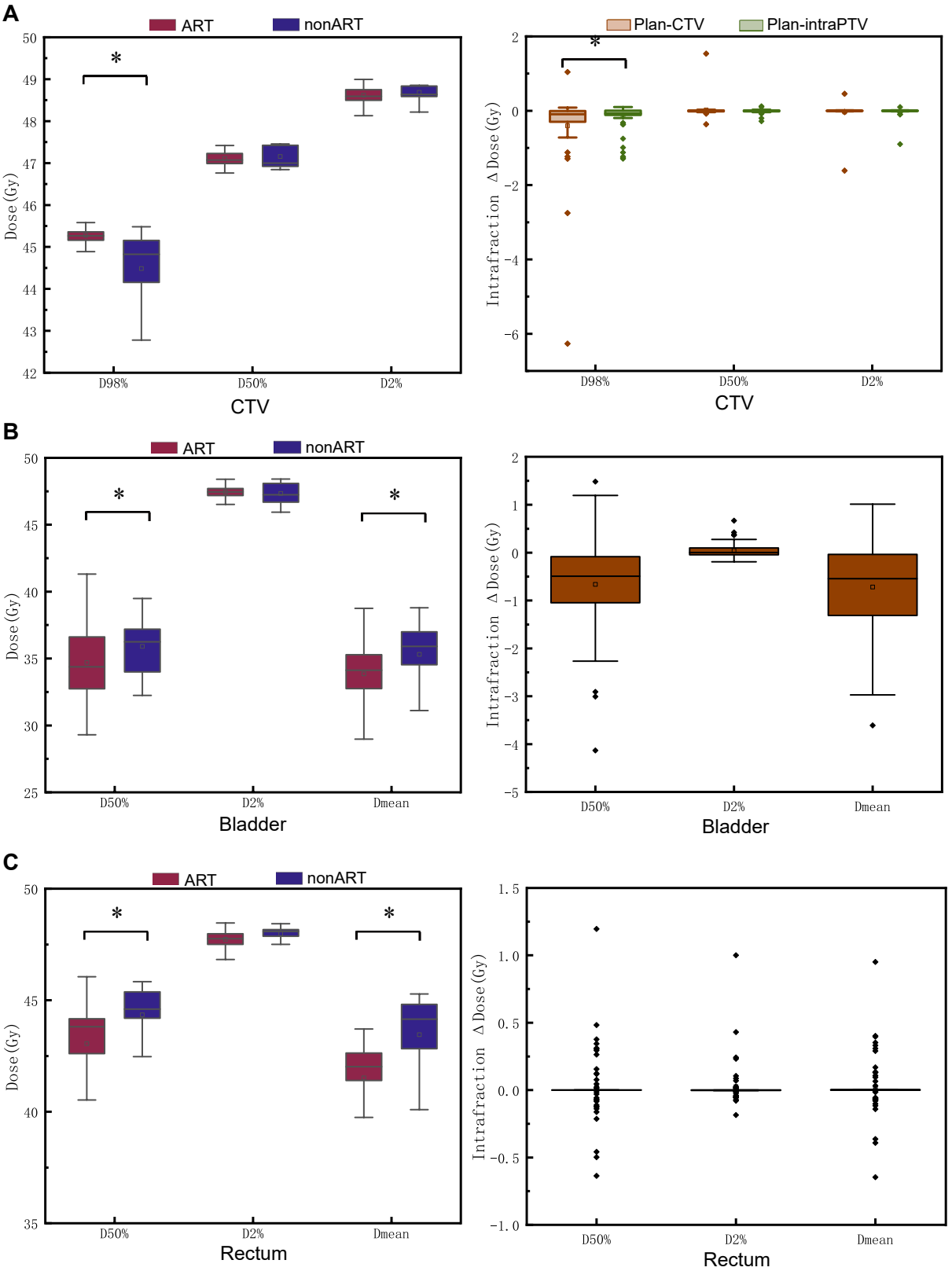

Fig. 6. The dosimetric comparison of CTV, bladder and rectum between ART and non-ART. (A) The left figure shows dosimetric comparison of CTV between ART and non-ART plans. The right figure shows intrafractional Δdose between Plan-CTV and Plan-intraPTV. A * indicates a significance of $P < 0.05$. (B) The left figure shows dosimetric comparison of bladder between ART and non-ART plans. The right figure shows intrafractional Δdose of bladder. A * indicates a significance of $P < 0.05$. (C) The left figure shows dosimetric comparison of rectum between ART and non-ART plans. The right figure shows intrafractional Δdose of rectum. A * indicates a significance of $P < 0.05$.

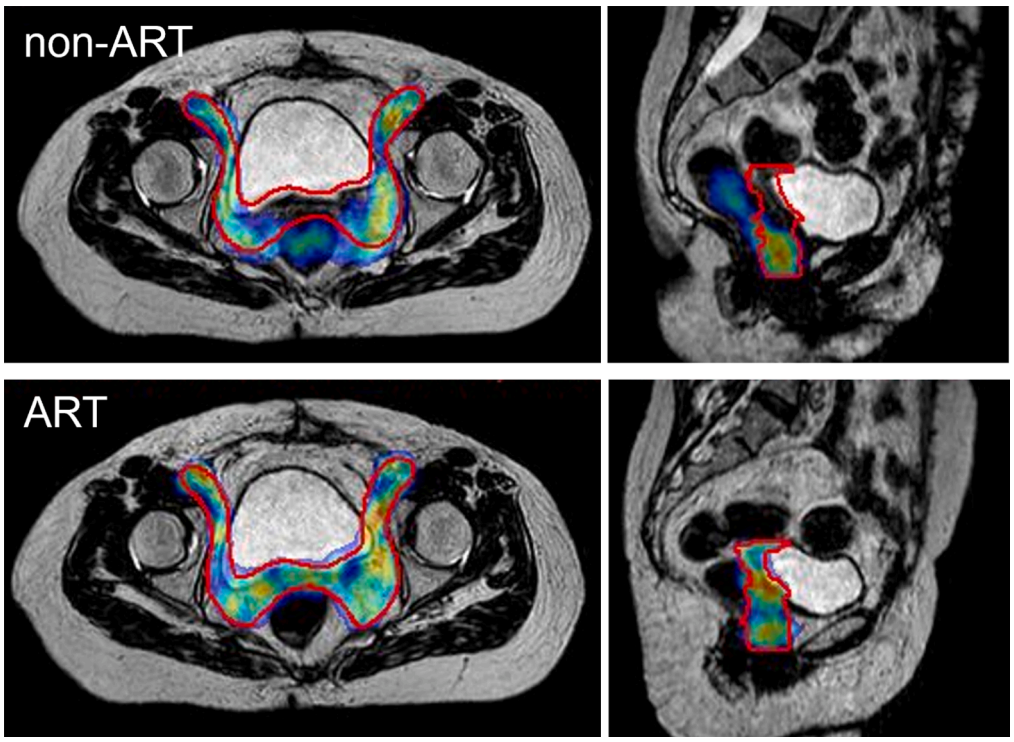

Fig. 7. The dose distributions for non-ART and ART plans of a representative case.

until end of RT) was 25.71 ± 6.73 min for patients with cervical cancers. During the treatment, the intrafractional changes of bladder, rectum and CTV may affect the actual dose received. In this study, we evaluated the intrafractional changes of structures and dose. The intrafractional process mainly included plan adaption and delivery, the mean time for them were 11.84 and 7.07 min, respectively. The mean intrafractional volume changes for CTV, bladder and rectum were −1.27 % (range: −13.39 % ~ 36.41 %), 20.83 % (range: −3.86 % ~ 96.78 %) and 0.15 % (range: −16.03 % ~ 18.48 %), respectively. The results revealed that these changes were mainly concentrated in the plan adaption stage. And we also observed the CTV motion trend during intrafractional time. The observation that the CTV motion increases with the time span can be attributed to the bladder volume increases over time, which is similar to the results published by Manger et al [21]. Additionally, the intrafractional bladder motion was affected by pretreatment volume and treatment time. The bladder with large intrafractional changes typically had corresponding long treatment time and small pre-treatment volume. For intrafractional dose changes, the mean changes of CTV $D_{98\%}$ were −0.27 ± 0.90 Gy and the mean changes of D_{mean} to bladder and rectum were −0.72 ± 0.94 Gy and 0.03 ± 0.20 Gy, respectively. The lower dose to bladder can be explained by the increase in bladder volume. Although the bladder volume increased during treatment, its impact on CTV was minimal. The cause could possibly lie in the directions of bladder filling. The bladder impacts the position of the bounded CTV only when it was filling towards the direction of CTV, i.e. the posterior-superior direction. Nonetheless, the progressive filling of the bladder in an anterior–superior direction effectively pushes away the small intestine during the therapeutic process. Similar results were observed for interfractional bladder filling by Van de Bunt et al. [9]. However, in this study, we found that there were still 15 % fractions failed in the CTV coverage constraints ($D_{98\%} \geq 45$ Gy) when evaluated with post-MRI. Intrafractional motion correction using 3 mm PTV margin, creates the possibility for further normal tissue sparing and CTV dose escalation in cervical cancer patients. Additionally, validation MRI scanned immediately before delivery and 2D MR motion monitoring could be used to validate the bladder motion. If large changes were observed during motion monitoring, the beam delivery could be terminated and a corrected treatment plan should be created.

Despite significant dosimetric benefit was observed for cervical cancer patients using MRI guided online ART, its practical implementation still remains arduous in a busy tertiary care center. The long treatment time might increase challenges in clinical practice, which could potentially lead to increased intrafractional movement, and further complicate accurate dose delivery changes. The treatment workflow will be optimized with the development of advanced technology including VMAT [22], AI based treatment planning [23] and contouring [24], and other automatic process, which will contribute to the benefit of MRI guided online ART. The concern regarding intrafractional motion is anticipated to diminish significantly with the integration of advanced technology in the future, which would effectively abbreviate treatment delivery times. The central limitation of this study is the number of patients. While it showcases significant potential in improving treatment accuracy and reducing side effects. Particularly our observations will be validated and refined with larger-scale and prospective studies.

Conclusions

Significant inter- and intrafractional variations of CTV and OARs were observed in patients with cervical cancer during the course of MRI-guided radiotherapy. A non-adaptive strategy led to inadequate target coverage for some individual patients in some fractions. MRI guided online adaptive radiotherapy could correct the day-to-day anatomical variations and ensure optimal target coverage for all fractions. Significant decrease of dose to bladder and rectum were observed when applying online adaptive radiotherapy. MRI guided online ART has significant dosimetric advantages in cervical cancer and is an ideal and clinical valuable approach for achieving individualized and precise radiotherapy.

CRediT authorship contribution statement

Shouliang Ding: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Zun Piao:** Data curation, Formal analysis, Methodology, Visualization. **Meining Chen:** Data curation, Formal analysis, Methodology, Visualization. **Fanghua Li:** Data curation, Methodology. **Yongbao Li:** Conceptualization, Formal analysis. **Biaoshui Liu:** Data curation. **Hongdong Liu:** Conceptualization, Methodology, Writing – review & editing. **Xiaoyan Huang:** Funding acquisition, Writing – review & editing. **Junyun Li:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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